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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,172	09/29/2003	Stephen Donovan	17510DIV2 (BOT)	5916

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,172	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/03, 12/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office action is responsive to Applicant's response filed March 29, 2006. Claims 1-21 and 31-35 have been cancelled. Claims 22-30 are under examination.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

3. The rejection is maintained for claims 22 and 26-29 under 35 U.S.C. 102(e) as anticipated by Yuzhakov et al for the reasons set forth on pages 2-3, paragraph 2 of the previous Office Action.

The rejection was on the grounds that Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition, which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference. The claim limitation " wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures" would be inherent in the teachings of the prior art.

Applicant's Arguments

Applicant urges that Yuzhakov et al (U.S. Patent 6,565, 522) cannot be used as anticipatory reference because the patent was granted after the filing of the claimed invention. Applicant urges that a reference can only be prior art under 102(e) if is granted before the priority date of the invention.

Examiner's Response to Applicant's Argument

Applicant's arguments filed March 29, 2006 have been fully considered but they are not persuasive.

It is the Examiner's position that Yuzhakov et al is an anticipatory reference under 35 U.S.C. 102(e). It should be remembered that the statute states that:

> (e) **the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent** or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The Examiner disagrees with Applicant's assertion that the "a reference can only be prior art under 102(e) if it is granted before the priority date of the invention". The statute requires that an application for patent **be filed** by another in the United States before the invention by the Applicant for patent. Therefore, 35 U.S.C. 102(e) does not require that the patent is granted. In view of all of the above, this rejection is maintained.

4. The rejection is maintained for claims 22 and 25-29 under 35 U.S.C. 103(a) as unpatentable over Yuzhakov et al in view of Mitragotri et al for the reasons set forth on pages 4-6, paragraph 3 of the previous Office Action.

The rejection was on the grounds that Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential
between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference.

Yuzhakov et al do not teach disrupting the stratum corneum by applying ultrasound at a frequency between 20 kHz and less than 10 Mhz at an intensity that does not permanently damage the patient's skin.

Mitragotri et al teach that ultrasound can mediate transdermal protein delivery by increasing the permeability of the human skin (see the Title and the Abstract). Mitragotri et al teach that low frequency ultrasound can induce significant transdermal transport of proteins including proteins between molecular weights of 6,000 and 48,000 (page 850). Mitragotri et al teach that application of ultrasound at therapeutic frequencies of about 1 MHz induces growth and oscillations of air pockets in the stratum corneum of human skin (page 850).

It would be *prima facie* obvious at the time the invention was made to use ultrasound to increase the permeability of the human skin because Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate for drug delivery and Mitragotri et al teach that low frequency ultrasound can induce significant transdermal transport of proteins including proteins between molecular weights of 6,000 and 48,000 (page 850). It would be expected barring evidence to the contrary, that the use of ultrasound at therapeutic frequencies would be effective in increasing the permeability of the human skin.

Applicant's Arguments

A) Applicant urges that the claims are nonobvious. Applicant urges that Yuzhakov et al (U.S. Patent 6,565, 522) cannot be used as primary reference in a 103 rejection because the patent was granted after the filing of the claimed invention. Applicant urges that none of the secondary references alone or in combination teach or suggest the claimed invention.

B) Applicant urges that the claimed invention recites steps of non-chemically disrupting the stratum corenum and applying a botulinum toxin to the disrupted stratum corenum for the botulinum toxin to penetrate to a subdermal layer of the patient skin. Applicant urges that the botulinum toxin is about 150 kDa by itself, and is about 900 kDa when it associated with other non-toxin proteins to form a complex. Applicant urges that Mitragotri et al do not teach or suggest a method of delivery of proteins having at least a molecular weight of 150 kDA much less a botulinum toxin.

Examiner's Response Applicant's Arguments

A) It is the Examiner's position that the combination of references (Yuzhakov et al in of Mitragorti et al) teach the claimed invention. To address Applicant's comments regarding Yuzhakov et al not being an appropriate reference, it is noted that the filing date (102(e)) for Yuzhakov et al is July 12, 2000 which is before Applicant's filing date of July 11, 2002.

B) It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention.

To address Applicant's comments regarding Mitragotri et al not teaching delivery of proteins having at least a molecular weight of 150 kDa, it should be noted that the Mitragotri et al acknowledge that ultrasound can be used to enhance transdermal transport of a few low molecular weight drugs across the skin (page 850). Mitragotri et al teach that low molecular weight is defined as drugs that are < 500. It should also be noted that Mitragotri et al teach that low ultrasound has been shown to increase the permeability of human skin to many drugs including high molecular weight proteins, by several orders of magnitude, thus making transdermal administration of these molecules potentially feasible (see the Abstract). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., specific molecular weights for drugs or compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

There is nothing on the record to show that the combination of references do not teach the claimed invention. In view of all of the above this rejection is maintained.

5. The rejection is maintained for claims 22-29 under 35 U.S.C. 103(a) as unpatentable over Yuzhakov et al, Mitragotri et al and further in view of Smith et al for the reasons set forth on pages 6-7, paragraph 4 of the previous Office Action.

The rejection was on the grounds that Yuzhakov et al and Mitragotri et al do not teach disrupting the stratum corneum by abrasively removing the stratum corneum.

Smith teaches that tape stripping is an effective barrier disruption method (column 16). Smith teaches that tape stripping vary widely with different individuals (column 16).

It would be *prima facie* obvious at the time the invention was made to abrasively disrupt the stratum corneum (e.g. tape stripping) because Smith teaches that tape stripping is an effective barrier disruption method and Yuzhakov et al teach small pressure of the microneedle arrays through the stratum corneum of the skin can delivery of drugs or facilitate biological fluid sampling (column 4). Yuzhakov et al teach that drugs can be deliver by way of passive diffusion (column 4). It would be expected barring evidence to the contrary, that the use of tape stripping would be effective in increasing the permeability of the human skin and thereby facilitating drug delivery.

Applicant's Arguments

A) Applicant urges that the claims are nonobvious. Applicant urges that Yuzhakov et al (U.S. Patent 6,565, 522) cannot be used as primary reference in a 103 rejection because the patent was granted after the filing of the claimed invention. Applicant urges that none of the secondary references alone or in combination teach or suggest the claimed invention.

B) Applicant urges that Smith et al do not teach or suggest that an enzyme such as botulinum toxin may be applied to the stripped skin area where the enzyme would penetrate to the subdermal layer of the skin. Applicant urges that one of ordinary skill in the art would not be motivated to apply a botulinum toxin to the stripped area of the skin because a retinoid and botulinum toxin are very different form each other and

would be expected to have different skin penetration properties. Applicant urges that vitamin A, a retinoid is about 0.30 kDa and botulinum toxin is about 150 –900 kDa.

Examiner's Response Applicant's Arguments

A) It is the Examiner's position that the combination of references (Yuzhakov et al, Mitragorti et al and Smith et al) teach the claimed invention. To address Applicant's comments regarding Yuzhakov et al not being an appropriate reference, it is noted that the filing date (102(e)) for Yuzhakov et al is July 12, 2000 which is before Applicant's filing date of July 11, 2002.

B) It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims require that a method of reducing neurotransmitter release in a subdermal structure of a patient comprising non-chemically disrupting the stratum corneum of a patient's skin to reduce the impermeability of the stratum corneum.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure and Mitragotri et al teach that low frequency ultrasound ultrasound has been shown to increase the permeability of human skin to many drugs including high molecular weight proteins, by several orders of magnitude, thus making transdermal administration of these molecules potentially feasible. However, Yuzhakov et al and Mitragotri et al do not teach disrupting the stratum corneum by abrasively removing the stratum corneum. Smith et al teach that tape stripping is an effective barrier disruption method. One of ordinary skill in the art would be motivated to use the tape stripping method as taught by Smith et al teach that by disrupting the skin barrier function the skin responds as though wounded and begins a generalized repair process increasing epidermal and dermal metabolism and angiogenesis of blood vessel formation under the control of skin signals released upon barrier disruption (column 8). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., specific molecular weights for drugs or compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

There is nothing on the record to show that the combination of references do not teach the claimed invention. In view of all of the above this rejection is maintained.

6. The rejection is maintained for claims 22 and 26-30 under 35 U.S.C. 103(a) as unpatentable over Yuzhakov et al in view of Cevc et al for the reasons set forth on pages 7-8, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4).
Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5). Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" is taught in the prior art reference.

Yuzhakov et al do not teach a method of reducing neurotransmitter release in a subdermal structure of a patient, wherein the botulinum toxin is incorporated into a transfersome.

Cevc teaches transfersome compositions comprising agents such as botulinum toxin D (column 31). Cevc teaches that the transfersome compositions of the invention can be introduced not only to a permeability barrier such as the skin, but moreover, can be transported into deeper tissues when they become systemically active (column 4, 66-67 and column 5, lines 1-4).

It would be *prima facie* obvious at the time the invention was made to use incorporated botulinum toxin into transfersomes as taught by Cevc because Cevc teaches that the transfersome compositions of the invention can be introduced to a permeability barrier such as the skin and can also be transported into deeper tissues when they become systemically active. It would be expected barring evidence to the contrary, that botulinum toxin compositions incorporated into transfersomes is a effective method of delivering botulinum toxin to skin thereby reducing neurotransmitter release in a subdermal structure in a patient.

Applicant's Arguments

A) Applicant urges that the claims are nonobvious. Applicant urges that Yuzhakov et al (U.S. Patent 6,565, 522) cannot be used as primary reference in a 103 rejection because the patent was granted after the filing of the claimed invention. Applicant urges that none of the secondary references alone or in combination teach or suggest the claimed invention.

B) Applicant urges that Cevc alone or in combination with the other secondary references fails to teach or suggest the step of non-chemically disrupting the a skin area in conjunction with the application of botulinum toxin much less that such step will allow for the botulinum toxin to penetrate to the subdermal layer of the skin.

Examiner's Response Applicant's Arguments

A) It is the Examiner's position that the combination of references (Yuzhakov et al and Cevc) teach the claimed invention. To address Applicant's comments regarding Yuzhakov et al not being an appropriate reference, it is noted that the filing date (102(e)) for Yuzhakov et al is July 12, 2000 which is before Applicant's filing date of July 11, 2002.

B) It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the

combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention.

The claims require that a method of reducing neurotransmitter release in a subdermal structure of a patient comprising non-chemically disrupting the stratum corneum of a patient's skin to reduce the impermeability of the stratum corneum and applying botulinum toxin to the skin of the patient in area that has had the stratum coreum disrupted. In this case, Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure. Mitragotri et al teach that low frequency ultrasound has been shown to increase the permeability of human skin to many drugs including high molecular weight proteins, by several orders of magnitude, thus making transdermal administration of these molecules potentially feasible. Smith et al teach that tape stripping a non-chemical method of disrupting the stratum corenum of a patient's skin. Cevc teaches that transfersomes can penetrate the skin to deliver compounds such as botulinum toxin to the skin. It would be expected barring evidence to the contrary, that the incorporation of botulinum toxin compositions into transfersomes and applying the compositions to areas of the skin that have been non-chemically disrupted would be an effective method of delivering botulinum toxin to skin thereby reducing neurotransmitter release in a subdermal structure in a patient.

There is nothing on the record to show that the combination of references do not teach the claimed invention. In view of all of the above this rejection is maintained.

Status of Claims

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
June 1, 2006

NITA MINNIFIELD
PRIMARY EXAMINER